HETEROCYCLES, Vol. 89, No. 8, 2014, pp. 1885 - 1891. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 11th May, 2014, Accepted, 16th June, 2014, Published online, 20th June, 2014
DOI: 10.3987/COM-14-13023

A NEW AND PRACTICAL SYNTHESIS OF 7-(3-CHLOROPROPOXY)-6-METHOXY-4-OXO-1,4-DIHYDROQUINOLINE-3-CARBONITRILE

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Abstract – New and improved synthetic route of bosutinib intermediate 7-(3-chloropropoxy)-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carbonitrile (**3**) is described on a hectogram scale. An intramolecular cyclization of 3-(2-aminophenyl)-3-oxopropanenitrile **11** with DMF-DMA to form the 4-oxo-1,4-dihydroquinoline-3-carbonitrile ring is adopted as the key step. Product **3** is obtained in 29.8% yield over eight steps and 98.6% purity (HPLC), which make it as a process of cost effective, environmentally friendly and feasible for scale-up operation.

Bosutinib (**1**, SKI-606, marketed as Bosulif ®, Figure 1) is a tyrosine kinase inhibitor undergoing research for use in the treatment of cancer.[1] Bosulif ® was originally developed by Wyeth Pharmaceuticals (merged to Pfizer in 2009) and received the US FDA and EU European Medicines Agency approval on September 4, 2012 and March 27, 2013 respectively for the treatment of adult patients with Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) with resistance, or intolerance to prior therapy.[2]

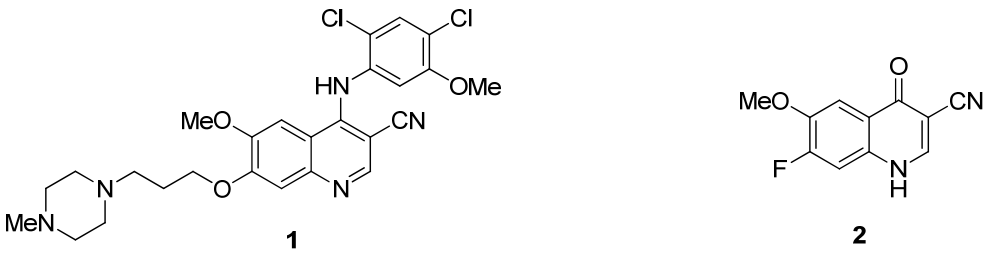
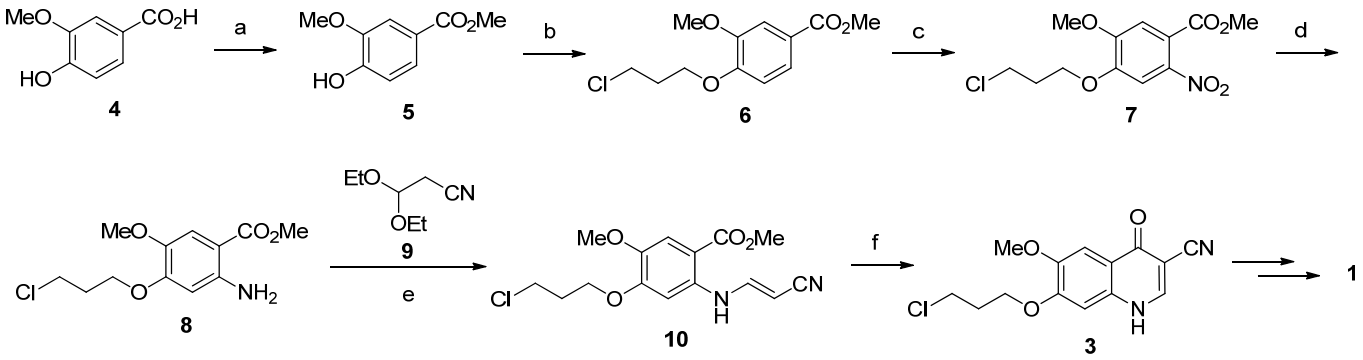


Figure 1. Chemical structures of bosutinib (**1**) and **2**

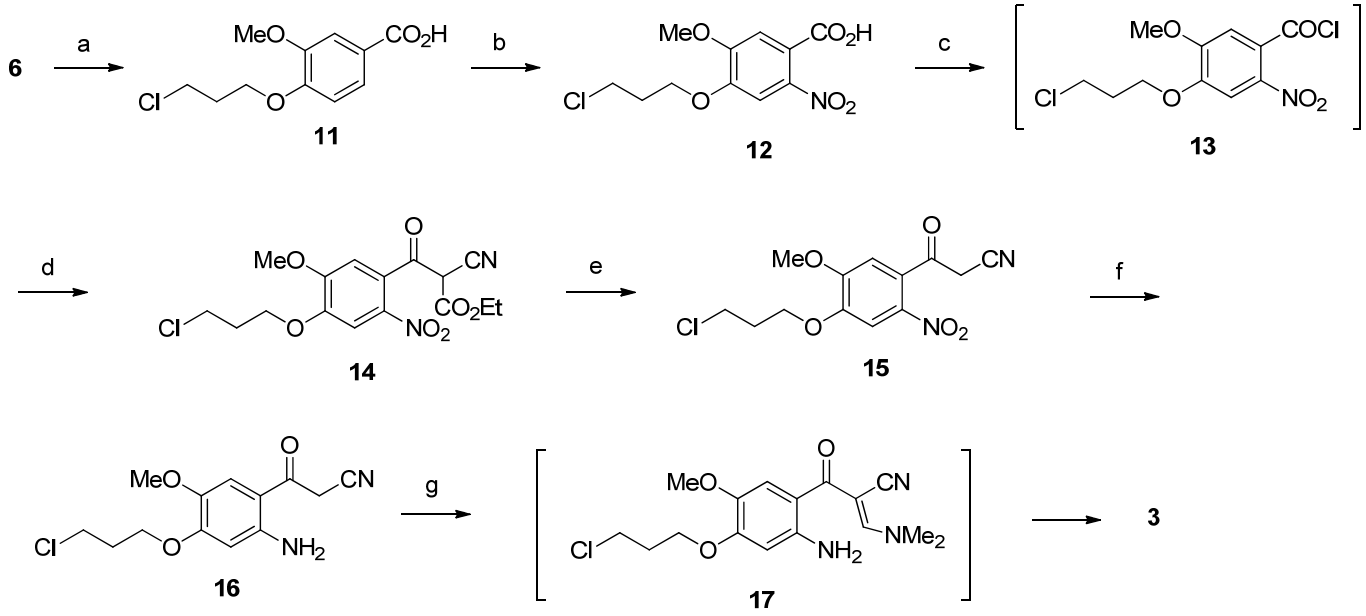
A couple of synthetic route of **1** were developed on a multi-grams scale, while a practical synthetic process is needed. The earlier and common work to prepare **1** was based on the Gould-Jacobs methodology through a thermal cyclization at 250 ºC for 4 h in Dowtherm A to synthesize the key intermediate 7-fluoro-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carbonitrile (**2**, Figure 1).[3] The main problem was that the high reaction temperature leaded to a messy and tedious operation and too many materials were destroyed in the reaction as tar or resin, which resulted in difficulties for purification and thus the overall yield was reduced dramatically (~ 40%). Withbroe *et al.*[4] developed a streamlined process for the synthesis and isolation of bosutinib monohydrate. Yin *et al.*[5] also reported a new synthesis of **1** that 7-(3-chloropropoxy)-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carbonitrile (**3**, Scheme 1) was adopted as the key intermediate. Vanillic acid (**4**) was used as the starting material, followed by esterification, alkylation, nitration, reduction, cyclization and so on.



Scheme 1. Reagents and conditions: (a) $SOCl_2$, MeOH; (b) ClC_3H_6Br, K_2CO_3, DMF; (c) HNO_3, AcOH; (d) Fe/NH_4Cl, MeOH-H_2O; (e) TFA; (f) NaOH, EtOH.

In order to develop a practical and commercial process of preparing compound **1**, a new and practical synthetic route was obtained, which adopted an intramolecular cyclization of 3-(2-aminophenyl)-3-oxopropanenitrile **16** with dimethylformamide dimethyl acetal (DMF-DMA) to form the key intermediate **3**, as shown in Scheme 2. Methyl vanillate (**5**) was used as the starting material, which was reacted with 1-bromo-3-chloropropane at K_2CO_3/DMF condition to give compound **6** in 91% isolated yield, based on the reported method.[5a] The benzoic acid **11** was obtained from **6** in 92% yield through the basic ester hydrolysis. The next nitration was carried out by HNO_3 in AcOH, compound **12** was obtained in 85% yield after recrystallization from MeOH. By treating **12** with oxalyl chloride and following reaction with ethyl cyanoacetate and NaOEt, compound **14** was achieved, which was purified by recrystallization from hexane/EtOAc in good yield (79%, two steps). Treatment of **14** with 90% DMSO in H_2O solution provided the compound **15** in 82% yield after recrystallization from hexane/EtOAc. The aniline **16** was obtained through catalytic hydrogenation of **15** under H_2/Raney Ni/THF condition at room

temperature. The crude **16** was purified by stirring in THF/MeOH, giving 91% overall yield and 96.9% purity (HPLC). The final cyclization of **16** was carried out in THF at room temperature by condensation with DMF-DMA to give the title compound **3**, most likely through the enaminoketonitrile intermediated **17** which could not be isolated by us so far. The crude **3** was purified by heating and stirring in 50% EtOH/EtOAc to give the compound with 71% overall yield. During the synthetic process research of ivacaftor[6] as well as the *N*-(3-cyano-7-ethoxy-4-oxo-1,4-dihydroquinolin-6-yl)acetamide as the key intermediate of neratinib,[7] the similar reductive cyclization method was developed by us.



Scheme 2. Reagents and conditions: (a) NaOH, MeOH-H_2O, 50 ºC, 12 h, 92%; (b) HNO_3, AcOH, 50 ºC, 6 h, 85%; (c) $(COCl)_2$, DMF (cat.), CH_2Cl_2, rt, 4 h; (d) $CNCH_2CO_2Et$, NaOEt, EtOH, 0 ºC, 79%; (e) DMSO-H_2O, 110 ºC, 0.5 h, 82%; (f) H_2, Raney Ni, THF, rt, 6 h, 91%; (g) DMF-DMA, THF, rt, 2 h, 71%.

In summary, we have developed a new and practical synthetic route of bosutinib intermediate **3** on a hectogram scale. Adopting the easily commercially available methyl vanillate (**5**) as the starting material, through the simple and traditional steps including alkylation, ester hydrolysis, nitration, decarboxylation, reduction, and cyclization to give the final product **3** in 29.8% yield over eight steps and 98.6% purity (HPLC). Purification methods of the intermediates involved in the route were also given.

ACKNOWLEDGMENT

This work was supported by the Special Scientific Foundation for Outstanding Young Teachers in Shanghai Higher Education Institutions (No. ZZGJD13017), the Scientific Research Foundation of Shanghai University of Engineering and Technology (SUES) (No. 2012-24), and the Undergraduate Innovative Training Project of SUES (No. cx1404020).

EXPERIMENTAL

All commercially available materials and solvents were used as received without any further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker UltraShield 400 Plus spectrometer using TMS as an internal standard. Mass spectra were obtained from a Finnigan MAT-95/711 spectrometer. The HPLC results were generated using a Waters 2487 UV/Visible Detector and Waters 515 Binary HPLC Pump.

Methyl 4-(3-chloropropoxy)-3-methoxybenzoate (6). 1-Bromo-3-chloropropane (404 g, 2.57 mol) was added dropwise to a stirred mixture of methyl vanillate (**5**, 360 g, 1.98 mol) and potassium carbonate (415 g, 3.0 mol) in DMF (1.8 kg) at 60 ºC. The reaction mixture was stirred at this temperature for another 1 h then cooled to room temperature, and poured slowly into ice-water (8 kg) while stirring constantly. The solid formed was filtered off and washed with cold water (0.8 kg × 2), dried at 60 ºC for 4 h. The white product was stirred and heated with 2:1 hexane/EtOAc (1 kg) at 60 ºC for 2 h then cooled to room temperature, the resulting solid was filtered off and washed with 2:1 hexane/EtOAc (300 g × 2), dried at 50 ºC for 4 h to afford **6** (466 g, 91%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (m, J = 6.4 Hz, 2H), 3.78 (t, J = 6.4 Hz, 2H), 3.90 (s, 3H), 3.91 (s, 3H), 4.23 (t, J = 6.0 Hz, 2H), 6.91 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 2.0, 8.4 Hz, 1H). ESI-MS (m/z) 281.0 $[M+Na]^+$.

4-(3-Chloropropoxy)-3-methoxybenzoic acid (11). A mixture of **6** (400 g, 1.55 mol), NaOH (80 g, 2.0 mol) in MeOH (2 kg) and H_2O (2 kg) was stirred and heated at 50–60 ºC for 12 h to form a clear solution. Until it was cooled to room temperature, H_2SO_4 was added slowly into the reaction solution to acidify to pH 2–3. The white suspension was stirred at the ambient temperature for 1 h. The resulting solid was filtered off and washed with H_2O (0.5 kg × 3) and MeOH (0.3 kg × 1), dried at 50 ºC for 5 h to give **11** (349 g, 92%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.19 (m, J = 6.0 Hz, 2H), 3.78 (t, J = 6.4 Hz, 2H), 3.81 (s, 3H), 4.15 (t, J = 6.0 Hz, 2H), 7.07 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 1.6 Hz, 1H), 7.55 (dd, J = 2.0, 8.4 Hz, 1H), 12.68 (s, 1H). ESI-MS (m/z) 267.0 $[M+Na]^+$.

4-(3-Chloropropoxy)-5-methoxy-2-nitrobenzoic acid (12). A stirred suspension of **11** (300 g, 1.23 mol), 65% HNO_3 (179 g, 1.85 mol) and AcOH (1.5 kg) was stirred at 40–50 ºC for 6 h to form a white solution. The mixture was poured slowly into ice water (5 kg) over 20 min and stirred. The resulting white solid was filtered, washed with H_2O (300 g × 3) and dried at 60 ºC for 5 h. The crude product was recrystallized from MeOH (0.7 kg) to afford **12** (303 g, 85%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (m, J = 6.0 Hz, 2H), 3.78 (t, J = 6.0 Hz, 2H), 3.92 (s, 3H), 4.23 (t, J = 6.0 Hz, 2H), 7.30 (s, 1H), 7.62 (s, 1H), 13.52 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 31.88, 42.17, 56.96, 66.59, 108.77, 111.97, 121.93, 141.89, 149.62, 152.43, 166.61. ESI-MS (m/z) 312.0 $[M+Na]^+$.

Ethyl 3-(4-(3-chloropropoxy)-5-methoxy-2-nitrophenyl)-2-cyano-3-oxopropanoate (14). $(COCl)_2$

(190 g, 1.5 mol) and DMF (7.3 g, 0.1 mol) were added respectively to a mixture of **12** (290 g, 1.0 mol) in CH_2Cl_2 (2 kg) at room temperature and the mixture was stirred for 4 h to form a homogeneous solution. The solvent was removed to give 4-(3-chloropropoxy)-5-methoxy-2-nitrobenzoyl chloride (**13**) as a light-brown oil.

A suspension of NaOEt (95 g, 1.4 mol) in anhydrous EtOH (0.8 kg) was stirred at 40–50 ºC for 1 h to get a solution firstly, and $CNCH_2CO_2Et$ (170 g, 1.5 mol) was added. The resulting white suspension was heated to reflux for another 0.5 h and then cooled to –5 ºC in an ice-salt bath and treated dropwise with **13** (1.0 mol) in THF (0.8 kg) over 2 h, keeping the reaction temperature below 0 ºC. The reaction mixture was then added to chilled water (6 kg), stirred and acidified to pH 2–3 with H_2SO_4. The resulting solid was collected by suction filtration, washed with H_2O (400 g × 3), and dried at 50 ºC for 5 h to give crude **14**, which was recrystallized from 3:1 hexane/EtOAc (1 kg) to afford **14** (304 g, 79%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J = 7.0 Hz, 3H), 2.23 (m, J = 6.0 Hz, 2H), 3.80 (t, J = 6.4 Hz, 2H), 3.87 (q, J = 7.0 Hz, 2H), 3.89 (s, 3H), 4.26 (t, J = 6.0 Hz, 2H), 7.09 (s, 1H), 7.78 (s, 1H), 10.35 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.32, 31.96, 42.20, 57.17, 60.00, 66.49, 80.85, 108.70, 111.86, 117.23, 127.75, 138.58, 148.34, 154.24, 164.17, 181.77. ESI-MS (*m*/*z*) 407.1 $[M+Na]^+$.

3-(4-(3-Chloropropoxy)-5-methoxy-2-nitrophenyl)-3-oxopropanenitrile (15). A mixture of **14** (300 g, 0.78 mol), DMSO (1.2 kg) and H_2O (100 g) was heated at 100–110 ºC for 30 min. Then the brown solution was cooled to around 50 ºC, poured into chilled water (4 kg), and stirred for 1 h. The resulting precipitate was collected by suction filtration, washed with H_2O (300 g × 3) and 50% EtOH/H_2O (200 g × 1), dried at 60 ºC for 4 h to give a brown solid, which was recrystallized from 1:1 hexane/EtOAc (0.8 kg) to afford **15** (200 g, 82%) as light-tan solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (m, J = 6.4 Hz, 2H), 3.79 (t, J = 6.8 Hz, 2H), 3.94 (s, 3H), 4.27 (t, J = 6.0 Hz, 2H), 4.52 (s, 2H), 7.32 (s, 1H), 7.76 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 31.75, 33.02, 42.06, 57.18, 66.57, 108.71, 110.67, 115.47, 128.97, 138.73, 149.41, 154.21, 191.71. ESI-MS (*m*/*z*) 335.0 $[M+Na]^+$.

3-(2-Amino-4-(3-chloropropoxy)-5-methoxyphenyl)-3-oxopropanenitrile (16). Compound **15** (180 g, 0.57 mol) and Raney Ni (wet, 30 g) were added to THF (3 kg), and stirred for 6 h at room temperature under H_2 atmosphere to form a clear brown solution. The reaction mixture was then filtered through a celite pad, the filter cake was washed by THF (250 g × 2). The combined filtrate was concentrated to give the product as a light-brown solid, which was stirred with 1:1 THF/MeOH (400 g) at room temperature for 2 h. The resulting precipitate was collected by suction filtration, washed with MeOH (150 g × 2), dried at 50 ºC for 2 h to afford **16** (147 g, 91%) as light-tan solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (m, J = 5.6 Hz, 2H), 3.71 (s, 3H), 3.79 (t, J = 5.6 Hz, 2H), 4.08 (t, J = 5.6 Hz, 2H), 4.54 (s, 2H), 6.40 (s, 1H), 6.98 (s, 1H), 7.17 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 30.31, 31.74, 42.33, 56.97, 65.33,

100.00, 107.27, 114.22, 116.88, 139.79, 149.94, 155.81, 187.77. ESI-MS (*m*/*z*) 305.1 $[M+H]^+$. HPLC Conditions: Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 280 nm; Flow rate: 0.8 mL/min; Temperature: rt; Injection load: 2 μL; Solvent: MeCN; Run time: 5 min; Mobile phase: MeCN /water = 80/20, t_R: 0.563 min, purity: 96.9%.

7-(3-Chloropropoxy)-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carbonitrile (3). To a stirred suspension of **16** (120 g, 0.42 mol) in THF (0.5 kg) was added DMF-DMA (65.7 g, 0.55 mol). The mixture was stirred at room temperature for 2 h to give a light-yellow suspension. H_2O (1.2 kg) was added to the reaction solution and stirred at room temperature for 1 h, the resulting solid was collected by suction filtration, washed with 50% EtOH/H_2O (100 g × 2), and dried at 60 ºC to give a grey solid. The product was stirred and heated with 1:1 EtOH/EtOAc (190 g) at 60 ºC for 2 h then cooled to room temperature, the resulting solid was filtered off and washed with 1:1 EtOH/EtOAc (50 g × 2), dried at 60 ºC for 4 h to afford **3** (87 g, 71%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (m, J = 3.2 Hz, 2H), 3.82 (t, J = 3.2 Hz, 2H), 3.88 (s, 3H), 4.19 (t, J = 3.6 Hz, 2H), 7.07 (s, 1H), 7.45 (s, 1H), 8.58 (s, 1H), 12.50 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 31.77, 42.23, 56.27, 65.89, 93.21, 101.54, 104.93, 117.62, 119.73, 135.18, 145.33, 148.54, 153.17, 173.77. ESI-MS (*m*/*z*) 315.1 $[M+Na]^+$. HPLC Conditions: Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 280 nm; Flow rate: 0.8 mL/min; Temperature: rt; Injection load: 2 μL; Solvent: acetonitrile; Run time: 5 min; Mobile phase: acetonitrile/water = 80/20, t_R: 0.490 min, purity: 98.6%.

REFERENCES

1. (a) M. Puttini, A. M. Coluccia, F. Boschelli, L. Cleris, E. Marchesi, A. Donella-Deana, S. Ahmed, S. Redaelli, R. Piazza, V. Magistroni, F. Andreoni, L. Scapozza, F. Formelli, and C. Gambacorti-Passerini, *Cancer Res.,* 2006, **66**, 11314; (b) A. Vultur, R. Buettner, C. Kowolik, W. Liang, D. Smith, F. Boschelli, and R. Jove, *Mol. Cancer Ther.,* 2008, **7**, 1185.
2. (a) J. E. Cortes, H. M. Kantarjian, T. H. Brummendorf, D. W. Kim, A. G. Turkina, Z. X. Shen, R. Pasquini, H. J. Khoury, S. Arkin, A. Volkert, N. Besson, R. Abbas, J. Wang, E. Leip, and C. Gambacorti-Passerini, *Blood,* 2013, **118**, 4567; (b) J. E. Cortes, D. W. Kim, H. M. Kantarjian, T. H. Brummendorf, I. Dyagil, L. Griskevicus, H. Malhotra, C. Powell, K. Gogat, A. M. Countouriotis, and C. Gambacorti-Passerini, *J. Clin. Oncol.,* 2012, **30**, 3486; (c) A. I. Daud, S. S. Krishnamurthi, M. N. Saleh, B. J. Gitlitz, M. J. Borad, P. J. Gold, E. G. Chiorean, G. M. Springett, R. Abbas, S. Agarwal, N. Bardy-Bouxin, P. H. Hsyu, E. Leip, K. Turnbull, C. Zacharchuk, and W. A. Messersmith, *Clin. Cancer Res.,* 2012, **18**, 1092.
3. (a) D. Berger, D. Boschelli, S. Johnson, and Y. Wang. U.S. Patent 20030212276 A1, Nov. 13, 2003; (b) K. T. Arndt, D. H. Boschelli, F. C. Boschelli, and M. M. Zaleska, PCT Int. Appl. WO 2004075898

A1, Sep. 10, 2004.

4. (a) G. J. Withbroe, C. Seadeek, K. P. Girard, S. M. Guinness, B. C. Vanderplas, and R. Vaidyanathan, *Org. Process Res. Dev.,* 2013, **17**, 500; (b) J. D. Olszewski, M. K. May, and D. M. Berger, U.S. Patent 20070208164 A1, Sep. 6, 2007; (c) K. W. Sutherland, G. B. Feigelson, D. H. Boschelli, D. M. Blum, and H. L. Strong, U.S. Patent 2005043537 A1, Feb. 24, 2005.
5. (a) X. Yin, G. Xu, X. Sun, Y. Peng, X. Ji, K. Jiang, and F. Li, *Molecules,* 2010, **15**, 4261; (b) F. Li, X. Yin, K. Jiang, X. Sun, and G. Xu, China Patent CN 101792416 A, Aug. 4, 2010.
6. Y. He, Q. Xu, W. Ma, J. Zhang, H. Sun, and J. Shen, *Heterocycles,* 2014, **89**, 1035.
7. (a) Q. Zhang, Y. Mao, Z. Liu, K. Xie, Y. Zhu, Y. Wei, and J. Shen, *Heterocycles,* 2011, **83**, 2851; (b) Y. Mao, J. Li, J. Zheng, Z. Liu, K. Xie, H. Li, J. Shi, Y. Li, and J. Shen, PCT Int. Appl. WO 2010045785, Apr. 29, 2010; (c) Y. Mao, J. Li, K. Xie, H. Li, R. Zhang, H. Duan, H. Guo, and J. Shen, PCT Int. Appl. WO 2009149622, Dec. 17, 2009; (d) Y. Mao, J. Li, J. Zheng, Z. Liu, K. Xie, H. Li, J. Shi, Y. Li, and J. Shen, U.S. Patent 20110263860, Oct. 27, 2011; (e) Y. Mao, Z. Liu, X. Yang, X. Xia, R. Zhang, J. Li, X. Jiang, K. Xie, J. Zheng, H. Zhang, J. Suo, and J. Shen. *Org. Process Res. Dev.*, 2012, **16**, 1970.